

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
25 October 2001 (25.10.2001)

PCT

(10) International Publication Number
WO 01/78738 A1

(51) International Patent Classification⁷: **A61K 31/575**,
31:167, A61P 11/06 // (A61K 31/575, 31:167)

(21) International Application Number: PCT/GB01/01629

(22) International Filing Date: 11 April 2001 (11.04.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0009607.3 18 April 2000 (18.04.2000) GB

(71) Applicant (for all designated States except US): **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **GAVIN, Brian, Charles** [IE/IE]; GlaxoSmithKline, P.O. Box 700, Grange Road, Rathfarnham, 16 Dublin (IE).

(74) Agent: **LEAROYD, Stephanie, Anne**; GlaxoSmithKline, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MEDICAL COMPOSITIONS COMPRISING (R,R)-FORMOTEROL AND ROFLEPONIDE

(57) Abstract: The present invention is concerned with pharmaceutical formulations comprising a combination of (R,R)-formoterol and rofleponide and the use of such formulations in medicine, particularly in the prophylaxis and treatment of respiratory diseases.



WO 01/78738 A1

MEDICAL COMPOSITIONS COMPRISING (R,R)-FORMOTEROL UND ROFLEPONIDE

The present invention is concerned with combinations of (R,R)-formoterol and rofleponide, particularly compositions containing a combination of (R,R)-formoterol and rofleponide and the use of such compositions in medicine, particularly in the prophylaxis and treatment of respiratory diseases.

Formoterol, i.e. 2'-hydroxy-5'-[(RS)-1-hydroxy-2{[(RS)-p-methoxy- α -methylphenethyl]amino}ethyl]formanilide, particularly its fumarate salt is a well-known adrenoreceptor agonist which is now used clinically in the treatment of bronchial asthma and related disorders. Formoterol includes two asymmetric centres and in a particular form exists as the (R,R)- isomer. The (R,R) isomer of formoterol has been described previously, for example, in WO98/21175 and US5795564.

WO 92/13872 describes rofleponide i.e. 16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β ,21-dihydroxypregn-4-ene-3,20-dione, salts and esters thereof and pharmaceutical formulations thereof. Rofleponide is an antiinflammatory corticosteroid, which is proposed for use in the treatment of bronchial asthma and related disorders.

WO 99/00134 describes combinations of formoterol and rofleponide but is silent as to the utility of (R,R)-formoterol.

Although formoterol fumarate and rofleponide may be effective therapies, there exists a clinical need for asthma therapies having potent and selective action and having an advantageous profile of action.

Therefore, according to the present invention there is provided a combination of (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and rofleponide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

It will be appreciated that the compounds of the combination may be administered simultaneously, either in the same or different pharmaceutical formulations or sequentially. If there is sequential administration, the delay in administering the second compound should not be such as to lose the beneficial therapeutic effect of the combination.

According to a further aspect of the present invention, there is provided a pharmaceutical formulation comprising (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and rofleponide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients. According to a preferred aspect of the present invention, there is provided a pharmaceutical formulation comprising (R,R)-formoterol fumarate and rofleponide palmitate, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients. In the most preferred aspect, the above pharmaceutical formulations are suitable for administration by inhalation.

It is to be understood that the present invention covers all combinations of particular and preferred aspects of the invention described herein.

As would be appreciated by the skilled person, rofleponide contains several asymmetric centres. The present invention includes each isomer of rofleponide, particularly the (22R) and (22S) isomers, either in substantially pure form or admixed in any proportions. The isomers of rofleponide have been described previously in WO 92/13872.

By the term "physiologically functional derivative" is meant a chemical derivative of (R,R)-formoterol or rofleponide having the same physiological function as the free compound, for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters.

Suitable salts according to the invention include those formed with both organic and inorganic acids. Pharmaceutically acceptable acid addition salts include but

are not limited to those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, succinic, oxalic, fumaric, maleic, oxaloacetic, methanesulphonic, ethanesulphonic, p-toluenesulphonic, benzenesulphonic, isethionic, and naphthalenecarboxylic, such as 1-hydroxy-2-naphthalenecarboxylic acids.

Pharmaceutically acceptable esters of (R,R)-formoterol or rofleponide may have a hydroxyl group converted to a C₁₋₆alkyl, aryl, aryl C₁₋₆ alkyl, or amino acid ester.

As mentioned above, both (R,R)-formoterol and rofleponide and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have been described for use in the treatment of respiratory diseases. Therefore, formulations of (R,R)-formoterol and rofleponide and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have use in the prophylaxis and treatment of clinical conditions for which a selective β_2 -adrenoreceptor agonist and/or an antiinflammatory corticosteroid is indicated. Such conditions include diseases associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease.

Accordingly, the present invention provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2 -adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated, which comprises administration of a therapeutically effective amount of a combination of (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and rofleponide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. The present invention further provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2 -adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated, which comprises administration of a therapeutically effective amount of a pharmaceutical formulation comprising (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative

thereof and rofleponide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient. In a preferred aspect, there is provided such a method which comprises administration of a therapeutically effective amount of a pharmaceutical formulation comprising (R,R)-formoterol fumarate and rofleponide palmitate, and a pharmaceutically acceptable carrier or excipient. In particular, the present invention provides such methods for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

In the alternative, there is provided a combination of (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and rofleponide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, for use in therapy, particularly for use in the prophylaxis or treatment of a clinical condition for which a selective β_2 -adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated. In particular, there is provided a pharmaceutical formulation comprising (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (suitably, (R,R)-formoterol fumarate) and rofleponide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (suitably, rofleponide palmitate), and a pharmaceutically acceptable carrier or excipient for use in therapy, particularly for use in the prophylaxis or treatment of a clinical condition for which a selective β_2 -adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated. In a preferred aspect, the invention is concerned with the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

The amount of (R,R)-formoterol and rofleponide, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated. As a monotherapy, (R,R)-formoterol

fumarate is generally administered to adult humans by aerosol inhalation at a dose of 12mcg or 24mcg twice daily. As a monotherapy, rofleponide is described in WO 92/13872 as being administered to adult humans by aerosol inhalation at a dose of from 10mcg to 1000mcg, preferably 20mcg to 250mcg.

5

While it is possible for the active ingredients of the combination to be administered as the raw chemical, it is preferable to present them as a pharmaceutical formulation. When the individual compounds of the combination are administered separately, they are generally each presented as a pharmaceutical formulation as described previously in the art.

10

Pharmaceutical formulations are often prescribed to the patient in "patient packs" containing the whole course of treatment in a single package. Patient packs have an advantage over traditional prescriptions, where a pharmacist divides a patient's supply of a pharmaceutical from a bulk supply, in that the patient always has access to the package insert contained in the patient pack, normally missing in traditional prescriptions. The inclusion of a package insert has been shown to improve patient compliance with the physician's instructions and, therefore, lead generally to more successful treatment. It will be understood that the administration of the combination of the invention by means of a single patient pack, or patient packs of each component compound, and containing a package insert instructing the patient to the correct use of the invention is a desirable additional feature of the invention.

15

20

25

Hereinafter, the term "active ingredients" means (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, preferably (R,R)-formoterol fumarate, and rofleponide, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, preferably rofleponide palmitate.

30

Suitably, the pharmaceutical formulations which are suitable for inhalation according to the invention comprise the active ingredients in amounts such that each actuation provides therapeutically effective dose, for example, a dose of (R,R)-formoterol of 10mcg to 150mcg, preferably 24mcg and a dose of rofleponide of 10mcg to 1.6mg, preferably 20mcg to 250mcg.

35

The pharmaceutical formulations according to the invention may further include other therapeutic agents for example anti-inflammatory agents such as other corticosteroids (e.g. fluticasone propionate, beclomethasone dipropionate, mometasone furoate, triamcinolone acetonide or budesonide) or NSAIDs (e.g. sodium cromoglycate, nedocromil sodium, PDE-4 inhibitors, leukotriene antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists), or other β_2 -adrenoreceptor agonists (such as salbutamol, salmeterol, fenoterol or terbutaline and salts thereof), or anticholinergic agents (such as ipratropium, or tiotropium).

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), intranasal, inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers or insufflators), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredients into association with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations for inhalation include powder compositions which will preferably contain lactose, and spray compositions which may be formulated, for example, as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,2-tetrafluoroethane, carbon dioxide or other suitable gas. Suitable aerosol formulations include those described in EP 0372777 and WO93/11743. For suspension aerosols, the active ingredients should be micronised so as to permit inhalation of substantially all of the active ingredients

into the lungs upon administration of the aerosol formulation, thus the active ingredients will have a particle size of less than 100 microns, desirably less than 20 microns, and preferably in the range 1 to 10 microns, for example, 1 to 5 microns.

5

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

10

Capsules and cartridges or for example gelatin, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator may be formulated containing a powder mix of the active ingredients and a suitable powder base such as lactose or starch. In this aspect, the active ingredients are suitably micronised so as to permit inhalation of substantially all of the active ingredients into the lungs upon administration of the dry powder formulation, thus the active ingredients will have a particle size of less than 100 microns, desirably less than 20 microns, and preferably in the range 1 to 10 microns.

15

20

Solutions for inhalation by nebulation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

25

Preferred unit dosage formulations are those containing a pharmaceutically effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient. Thus, in the case of formulations designed for delivery by metered dose pressurised aerosols, one actuation of the aerosol may deliver half of the therapeutically effective amount such that two actuations are necessary to deliver the therapeutically effective dose.

30

35

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question. Furthermore, the claimed formulations include bioequivalents as defined by the US Food and Drugs Agency.

For a better understanding of the invention, the following Examples are given by way of illustration.

5 EXAMPLES

A: Metered Dose Inhalers

 Example 1

	Per actuation
(R,R)-formoterol fumarate	24 microgram
Rofleponide	200 microgram
1,1,1,2-Tetrafluoroethane	to 75.0mg

10

The micronised active ingredients are weighed into an aluminium can, 1,1,1,2-tetrafluoroethane is then added from a vacuum flask and a metering valve is crimped into place.

15 Similar methods may be used for the formulation of Example 2:

 Example 2

	Per actuation
(R,R)-formoterol fumarate	12 microgram
Rofleponide	100 microgram
1,1,1,2-Tetrafluoroethane	to 75.0mg

20

25

B: Dry Powder Inhalers

Example 3

	Per cartridge or blister
(R,R)-formoterol fumarate	24 microgram
Rofleponide	200 microgram
Lactose Ph. Eur.	to 12.5mg or to 25.0mg

- 5 The active ingredients are micronised and bulk blended with the lactose in the proportions given above. The blend is filled into hard gelatin capsules or cartridges or in specifically constructed double foil blister packs to be administered by an inhaler such as a Rotahaler, Diskhaler, or Diskus inhaler (each of these being a Trademark of Glaxo Group Limited).

10

Similar methods may be used for the formulations of Example 4:

Example 4

	Per cartridge or blister
(R,R)-Formoterol fumarate	12 microgram
Rofleponide	100 microgram
Lactose Ph. Eur.	to 12.5mg or to 25.0mg

15

Claims

1. A pharmaceutical formulation comprising (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and rofleponide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.
2. A pharmaceutical formulation comprising (R,R)-formoterol fumarate and rofleponide palmitate, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.
3. A pharmaceutical formulation according to claim 1 or claim 2 which comprises another corticosteroid, another β_2 -adrenoreceptor agonist or an anticholinergic agent.
4. A pharmaceutical formulation according to claim 3, wherein the other β_2 -adrenoreceptor agonist is salbutamol, salmeterol, fenoterol, terbutaline, or a salt thereof.
5. A pharmaceutical formulation according to claim 3 wherein the anticholinergic agent is ipratropium or tiotropium.
6. A pharmaceutical formulation according to any one of claims 1 to 6 which is suitable for administration by inhalation.
7. A pharmaceutical formulation according to any one of claims 1 to 6 which is suitable for intranasal administration.
8. A pharmaceutical formulation consisting of (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and rofleponide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and optionally one or more other therapeutic ingredients, and 1,1,1,2 - tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane or mixtures thereof as propellant.

9. A method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2 -adrenoreceptor agonist and/or an antiinflammatory corticosteroid is indicated, which comprises
5 administration of a therapeutically effective amount of a pharmaceutical formulation according to any one of claims 1 to 9.
10. A method according to claim 11 wherein the clinical condition is a disease
10 associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/GB 01/01629

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/575 A61K31/167 A61P11/06 //(A61K31/575,31:167)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, MEDLINE, BIOSIS, CHEM ABS Data, EMBASE, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 00134 A (ASTRA AB) 7 January 1999 (1999-01-07)	1-10
Y	claims 1-17	1-10
Y	WO 98 21175 A (SEPRACOR INC) 22 May 1998 (1998-05-22) cited in the application claims 19-21	1-10
Y	US 5 795 564 A (MORLEY JOHN ET AL) 18 August 1998 (1998-08-18) cited in the application abstract	1-10
Y	WO 92 13872 A (ASTRA AB) 20 August 1992 (1992-08-20) cited in the application claims 1-11	1-10
	--- -/--	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

8 August 2001

Date of mailing of the international search report

04/09/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Herrera, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/01629

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	O'CONNOR B J: "COMBINATION THERAPY" PULMONARY PHARMACOLOGY AND THERAPEUTICS, ACADEMIC PRESS, NEW YORK, NY, US, vol. 11, no. 5/6, 1998, pages 397-399, XP000911059 ISSN: 1094-5539 the whole document -----	1-10
Y	BOWLER S: "LONG ACTING BETA AGONISTS" AUSTRALIAN FAMILY PHYSICIAN, XX, XX, vol. 27, no. 12, December 1998 (1998-12), pages 1115,1117-1118, XP000973076 the whole document -----	1-10

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/01629

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9900134	A	07-01-1999	AU 8135098	A	19-01-1999
			BR 9810452	A	05-09-2000
			EE 9900594	A	15-08-2000
			EP 1009408	A	21-06-2000
			HU 0002533	A	28-12-2000
			NO 996438	A	28-02-2000
			PL 337722	A	28-08-2000
			SK 184799	A	12-06-2000
			TR 9903272	T	21-08-2000
WO 9821175	A	22-05-1998	AU 722859	B	10-08-2000
			AU 5175598	A	03-06-1998
			EP 0938467	A	01-09-1999
			US 6040344	A	21-03-2000
US 5795564	A	18-08-1998	US 6068833	A	30-05-2000
WO 9213872	A	20-08-1992	AP 366	A	21-10-1994
			AT 178611	T	15-04-1999
			AU 661471	B	27-07-1995
			AU 1230792	A	07-09-1992
			BG 62211	B	31-05-1999
			BG 97971	A	25-04-1994
			CA 2103924	A	05-08-1992
			CN 1064079	A, B	02-09-1992
			CN 1140178	A, B	15-01-1997
			CN 1140059	A, B	15-01-1997
			CZ 9301496	A	16-03-1994
			DE 69228870	D	12-05-1999
			DE 69228870	T	19-08-1999
			DK 570454	T	18-10-1999
			EE 3111	B	15-04-1996
			EP 0570454	A	24-11-1993
			ES 2133315	T	16-09-1999
			FI 933450	A	03-08-1993
			GR 3030657	T	29-10-1999
			HK 1010733	A	24-03-2000
			HU 64973	A, B	28-03-1994
			IE 920166	A	12-08-1992
			IL 100532	A	14-05-1996
			JP 6505232	T	16-06-1994
			KR 216720	B	01-10-1999
			MX 9200324	A	01-09-1992
			NO 304073	B	19-10-1998
			NZ 241210	A	26-08-1993
			PL 170000	B	31-10-1996
			PT 100086	A, B	31-05-1994
			RO 111195	B	30-07-1996
			RU 2111212	C	20-05-1998
			SG 52557	A	28-09-1998
			SI 9210065	A	28-02-1995
			SK 79693	A	09-03-1994
			US 5674861	A	07-10-1997
			US 5939409	A	17-08-1999
			ZA 9200233	A	28-10-1992